On page 18, line 20 , please replace with:

---Target No. 3: PVVPRQEQLL (**SEQ. ID. NO. 11**) & FLNEDGPLLA (**SEQ. ID. NO. 12**)---

On page 18, line 21 , please replace with:

---Target No. 4: FSCSLPIR (**SEQ. ID. NO. 13**) & GIPVSCRF (**SEQ. ID. NO. 14**)---

REMARKS

The application and claims have been amended to refer to updated sequence identifiers in conjunction with Applicant's response to the Notice to Comply mailed December 5, 2001. A marked-up copy of the original page of the application bearing the modified paragraph reflect the amendments in red ink.

Submitted herewith are substitute paper and computer readable copies of the Sequence Listing. An executed statement under 37 C.F.R 1.821(f) and (g) that the paper and computer readable copies of the Sequence Listing are identical and that the substitute Sequence Listing does add new matter is submitted herewith.

The amendments to the specification to add sequence identifiers and the Sequence Listing were made to correct several informalities. As such no new matter has been added and entry of the amendments and Sequence Listing is respectfully requested.

containing one or more peptide fragments having affinity for other peptide fragments of the same or substantially the same amino acid sequence. The polymerization domain determines the configuration of the multimeric protein complex (*e.g.*, as dimer, trimer, tetramer, pentamer, or others). Examples of polymerization domains include, but are not limited to, coiled-coil domains such as described and defined in Lupas *et al.*, 1991, Science 252:1162-1164, and alpha-helical sequences as described and defined in Eisenberg, D. *et al.*, (1986) Protein 1:16-22, Ho and DeGrado (1987) J.A.Chem.Soc. 109:6751-6758, Regan and DeGrado, (1988) Science 241:976-978, and Hill *et al.*, (1990) Science 249:543-546. A polymerization domain can be a naturally occurring peptide or can be designed and synthesized artificially. A naturally occurring polymerization domain may be modified to generate other polymerization domains (*see* Harbury *et al.* Science 262:1401-1407, 1993). In even more preferred embodiments, the coiled-coil domain comes from the leucine zipper region of transcription factor GCN4, the tetramerization domain of p53, or the N-terminal residues (aa 20-80) of cartilage oligomeric matrix protein. In another even more preferred embodiment, the alpha-helical sequences contain single helices or helix-turn-helix as summarized in Plückthun and Pack, (1997) Immunotechnology 3:83-105, incorporated by reference herein.

HRV bind to ICAM-1 in four regions. In preferred embodiments, the multivalent peptides bind to three or more (preferably four or more) amino acids in the following regions of human ICAM-1. These are referred to as the target sequences or target peptides hereinafter:

Target No. 1: Residues 1-5: QTSVS

Target No. 2: Residues 24-29: SCDQPK

Target No. 3: Residues 40-49: KELLLPGNNR

Target No. 4: Residues 70-77: PDGQSTAK

The multivalent recombinant antibodies and peptides of this invention bind to cellular receptors for rhinovirus with high affinity. In a preferred embodiment, they have an apparent affinity constant for the cellular receptors of no less than 10^8 M^{-1}. In a further preferred embodiment, they have an apparent affinity constant for the cellular receptors of no less than 10^9 M^{-1}. In an even further preferred embodiment, they have an apparent affinity constant for the cellular receptors of no less than 10^{10} M^{-1}.

By "apparent affinity constant" is meant the ratio of [Ab-Ag]/[Ab][Ag] when the antibody-antigen binding reaction reaches equilibrium. [Ab-Ag], [Ab], [Ag] are the

ICAM-1 and LDLR used to raise antibody in this invention can be of any species origin as long as the antibody raised is able to reduce the binding of HRV to their human host cells.

C. Cloning the single chain Fv (scFv) region of the mAb and humanizing the antibody

Single chain Fv fragments against ICAM-1 and LDLR are cloned from hybridomas against each antigen.

One way (a preferred way) of cloning the VH and VL fragments is to amplify them by polymerase chain reaction (PCR) from a hybridoma directed against ICAM-1 or LDLR. Alternatively, the Fab fragment of the desired antibody can be cloned from a combinatorial immunoglobulin library in phage λ by panning using the purified ICAM-1 and LDLR as the antigens (Kang *et al.*, 1991, Methods 2:111-118; Barbas and Lerner, 1991, Methods 2:119-124). The polypeptides of VH and VL can be connected via a synthetic linker to form a single-chain Fv fragment (scFv), or one scFv fragment can dimerize with another to form either diabodies (Holliger *et al.*, 1993, Proc. Natl. Acad. Sci. USA 90:6444-6448) or chelating recombinant antibodies (CRAbs) (Neri *et al.*, 1995, J. Mol. Biol. 246:367-373).

The amino acid sequences of the VH and VL domains can be modified based on the original antibody to increase the affinity to antigens or improve the yield of production in E coli or yeast. The origin of the antibody can be of any mammals, including, but are not limited to, human, mouse, rat and rabbit. When the original antibody is isolated from a species other than human, the VH and VL domains of the antibody can be humanized, such as using the methods in U.S. Patent 5,530,101.

Total RNA is isolated from each hybridoma and is converted into cDNA by AMV reverse transcriptase. The VH and VL genes are amplified by PCR using different combinations of degenerate primers in the Ig-Primer kit (Novagen, WI) according to the manufacturer's protocol, or using the primers as described in Larrick & Fry, 1991, Methods 2:106-110. The resulting VH and VL fragments are cloned into a TA cloning vector (Invitrogen, CA) and sequenced. The sequences of multiple clones are compared and the consensus sequences are used to construct the scFv fragments. The VH and VL genes are linked by an artificial linker $(GGGGS)_3$ to form scFv fragment [VH-$(GGGGS)_3$-VL] as in Batra *et al.*, 1990, and the scFv fragment is subcloned into a pBlueScript vector (Stratagene, CA). Methods of making svFv fragment are also described in U.S. Patents 5,571,894 and 5,608,039.

(SEQ. ID. NO 5)

The cloned scFv sequence can be humanized to make it less immunogenic or nonimmunogenic to a human host. The humanization of antibody can be carried out as described in U.S. Patent 5,530,101. The sequences of scFv fragments can also be modified to increase the yield of production while still maintaining their antigenic specificity, such as changing the genetic codons or including a signal sequence as described in U.S. Patent 5,648,237.

D. Constructing multivalent recombinant antibody genes

Methods of making multivalent recombinant antibodies are summarized in Plückthun and Pack, (1997) Immunotechnology 3:83-105, incorporated by reference herein.

A pentavalent recombinant antibody is preferred. scFv fragments are linked with the pentamerization domain of COMP via a hinge region (SEQ. ID. NO 6) to give rise to the following fragment: scFv-hinge[$(PQ)_2$ $PK(PQ)_4$ $PKPQPK(PE)_2$]-Pentamerization domain (COMP aa 28-72).

The pentamerization domain of COMP is amplified from plasmid p3b-COMP (Efimov *et al.*, 1994, FEBS letters 341:54-58) by PCR (Tomschy *et al.*, 1996, EMBO J. 14:3507-3514). The amino acid sequence of this COMP domain can be modified to increase the stability of the complex. For example, the Lys-29 and Ala-30 can be changed to cysteine residues (Terskish *et al.*, 1997, Proc. Natl. Acad. Sci. USA 94:1663-1668).

There are numerous sequences known to those skilled in the art as suitable for the hinge region. Therefore, the one listed here is only an example. The COMP pentamerization domain can be linked with the hinge and scFv by PCR and ligation using the standard molecular biology techniques. The whole fragment is subcloned into pTrc/His vector (Invitrogen, CA) to generate a bacteria expression plasmid pTrc/scFv-COMP.

E. Expressing multivalent recombinant antibodies in *E. coli*

The scFv-comp protein is expressed in *E. coli* as described in Terskiskh *et al.*, 1997, Proc. Natl. Acad. Sci. USA 94:1663-1668. Briefly, *E. coli* transformed with the plasmid pTrc/scFv-COMP is grown in culture until OD600 = 0.5, then 1 mM isopropyl b-D-thiogalactoside is added to induce protein synthesis, followed by a 4 hr incubation at 30^0C. Bacteria are harvested by centrifugation, lysed by three-rounds of freezing/thawing. The recombinant antibody protein is purified from the bacterial lysate by a nickel column (Qiagen).

Sequences carried by the selected phage are then determined using the Sequenase kit (United States Biochemical) with the primer 5'-CCCTCATAGTTAAGCGTAACG-3'(Koivunen, E. *et al.* (1993) J. Bio. Chem. 268:20205-20210). (SEQ. ID. NO 15)

Example 4: Identifying binding peptides to the target sequences in human ICAM-1 by molecular recognition theory and target complementary library technology (TCLT)

According to the molecular recognition theory, peptides with opposite hydropathic profiles bind to each other. One example is that a pair of peptides encoded by the sense and anti-sense strands of DNA bind to each other specifically (*see* Provisional Application Serial No. 60/083046 filed April 24, 1998, incorporated by reference herein in its entirety; and Blalock, J. E. (1990) TIBTECH 8:140-144), and they are known as complementary peptides.

Complementary peptides to the target sequences in human ICAM-1 are encoded by the antisense strand of human ICAM-1 gene in either 5'-3' or 3'-5' orientation. Therefore, for each target peptide, there are two complementary sequences, and both have specific affinity for the target peptide. The sequences of the complementary peptides for each target sequence in human ICAM-1 are listed in the following:

(SEQ. ID. NO 7) Target No. 1: VCRHR & GHRCL (SEQ. ID. NO 8)

(SEQ. ID. NO 9) Target No. 2: LGLVTG & RTLVGF (SEQ. ID. NO 10)

(SEQ. ID. NO 11) Target No. 3: PVVPRQEQLL & FLNEDGPLLA (SEQ. ID. NO 12)

(SEQ. ID. NO 13) Target No. 4: FSCSLPIR & GIPVSCRF (SEQ. ID. NO 14)

These complementary peptides (and their homologs) and peptides containing such may have the ability to bind to human ICAM-1 molecule at the target sequences. The affinity of a complementary peptide to its target sequence can be improved by optimizing the peptide sequence via a computer program, or by selecting peptides from a target complementary peptide library as described in Provisional Application Serial No. 60/083046.

Example 5: Construction of multivalent peptides against human ICAM-1

One way of making a multivalent peptide is to link multiple copies of a single peptide or multiple copies of different peptides in tandem repeats to create molecules with the following structures:

[peptide A-(linker)-]$_n$ (n >or= 2) or

[peptide A-(linker)-peptide B-(linker)-]$_n$ (n >or= 2)